UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/412,297	10/05/1999	KANG TING	3100.006US0	9486

44955 7590 09/13/2005

SQUIRE, SANDERS & DEMPSEY L.L.P.
1 MARITIME PLAZA, SUITE 300
SAN FRANCISCO, CA 94111

EXAMINER	
FORD, VANESSA L	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 09/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/412,297	TING, KANG	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7 June 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-52 and 54* is/are pending in the application.

4a) Of the above claim(s) *3-7 and 13-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 8-12 and 51-52 and 54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 March 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

FINAL ACTION

1. This Office Action is responsive to Applicant's amendment filed June 7, 2005. This Office Action is also responsive to Applicant's responses filed May 5, 2005 and June 7, 2005. Claims 1, 51 and 52 have been amended. Claim 53 has been cancelled. Claims 3-7 and 13-50 have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Claim 54 has been added.

2. The text of those sections of the Title 35, U.S. code not included in this action can be found in the prior Office Action.

Rejections Maintained

3. The rejection under 35 U.S.C. 112, first paragraph is maintained for claim 52 for the reasons set forth on pages 2-8 paragraph 3 of the previous Office Action.

The rejection was on the grounds that the claims are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of screening for an agent that modulates bone mineralization, said method comprising contacting an osteogenic cell selected from the group consisting of an osteroblast, a mesenchymal, a fibroblast cell, a dura cell, a chondrocyte, a chondreoblast and a MC3T3 cell expressing a Nell-1 gene with a test agent and detecting an expression level of said Nell-1 gene in the contacted cell where a difference in the expression level of Nell-1 in the contacted cell compared to an expression level of Nell-1 in a cell that is not contacted indicates that said test agent is an agent that modulates bone mineralization does not reasonably provide enablement for claimed method of screening for an agent that modulates bone mineralization, wherein the method comprising contacting an osteogenic cell selected from the group consisting of a stem cell and a bone marrow cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification teaches that Nell-1 expression is increased in fetal calvarial cells associated with bone formation in calvarial osteoblast-like cells in the fetus (page 42). The specification teaches that premature cranial suture closure as seen in craniosynostosis (CS) may be due to overproduction of cranial bone and therefore possibly but not definitively associated with the over-expression of the Nell-1 molecule (page 42). The specification teaches that Nell-1 mRNA was faintly expressed from day 14 of gestation with mild increase over gestation period and at day 14 is the time point when fetal calvaria starts to mineralize (page 42). The specification states "as a possible role of Nell-1, these proteins may act as a modulator interacting with other growth factors. The specification teaches that since TGFβ-1 is known as a regulator of osteogenesis, Nell-1's effect in enhancing mineralization may be related to its interaction with the TGFβ superfamily (page 43). The specification speculates on the function of Nell-1 based on the observation that it's expression is increased in fetal calvarial osteoblast-like cells. Although the specification teaches the use of "bone progenitor cells" which refer to any or all cells that have the capacity to ultimately form or contribute to the formation of new bone tissue (page 33).

The teachings of the cited art regarding bone progenitor cells as they relate to the claimed invention are cited below:

Bellows et al *(Developmental Biology, 133, 8-13, 1989)* teach that fetal or calvaria has become a standard model for bone cell metabolism (page 8). Bellows et al teach that isolated populations express osteoblastic properties comprise a heterogenous mixture of cell which include fibroblasts, chondrocytes, undifferentiated mesenchymal cells and cell at various stages of osteoblast differentiation (page 8). Bellows et al teach that precursors of osteogenic cell are believed to be derived from stem cells (page 12). Peterson et al *(U. S. Patent No. 6,200,606 B1, published March 13, 2001)* teach that the process of biological differentiation, which underlies the diversity of cell types exhibited by bone marrow, is the general process by which specialized, committed cell types arise from less specialized, primitive cell types (column 2). Peterson et al teach that differentiation may conveniently be thought of as a series of steps along a pathway, in which each step is occupied by a particular cell type potentially having unique genetic and phenotypic characteristics (column 2). Peterson et al teach that in the typical course of differentiation a pluripotent stem cell proceeds through one or more intermediate stage cellular divisions, ending ultimately in the appearance of one or more specialized cell types, such as T lymphocytes and osteocytes (column 2). Peterson et al teach that the uncommitted cell types which precede the fully differentiated forms, and which may or may not be true stem cells, are defined as precursor cells (column 2). Peterson et al teach that the precise signals that trigger differentiation down a particular path are not fully understood, it is clear that a variety of chemotactic, cellular, and other environmental signals come into play and within the mesenchymal lineage, for example, mesenchymal stem cells (MSC) cultured in vitro can be induced to differentiate into bone or cartilage *in vivo* and *in vitro*, depending upon the tissue environment or the culture medium into which the cells are placed (column 2). Peterson et al also teach that marrow also has the capacity to regenerate bone and other mesenchymal tissue types when implanted *in vivo* in

diffusion chambers (column 1). Peterson et al teach that results of this nature have led to the conclusion that bone marrow contains one or more populations of pluripotent cells, known as stem cells, having the capacity to differentiate into a wide variety of different cell types of the mesenchymal, hematopoietic, and stromal lineages (column 1). Caplan et al, *(U.S. Patent No. 5,486,359, published January 23, 1996)* teach that isolated human mesenchymal stem cells can differentiate into more than one tissue type (e.g. bone, cartilage, muscle or marrow stroma) (see the Abstract). Wobus *(Molecular Aspects of Medicine (2001), 22/3 (149-164)* teach that embryonic stem cells are pluripotenet cell line established from undifferentiated embryonic cells characterized by nearly unlimited self-renewal and differentiation capacity (see the Abstract). Zhang et al *(The Journal of Clinical Investigation, September 2002, Volume 110, Number 6)* teach that osteogenic fronts of abnormally closing/closed sutures in animals revealed calvarial overgrowth and overlap along with increase osteoblast differentiation and reduced cell proliferation (see the Abstract). Zhang et al teach that anomalies were restricted to calvarial bone, despite generalized, non-tissue-specific over-expression of Nell-1 (see the Abstract). Therefore, the claimed method requires calvarial bone cells.

The cited art has taught that a) osteoblastic cells are believed to be derived from stem cells but it has not been proven, b) mesenchymal stem cells and embryonic stem cells can differentiate into more than one tissue type including one, cartilage, muscle or marrow stroma and c) precise signals that trigger differentiation down a particular path are not fully understood, d) bone marrow contains one or more populations of pluripotent cells, known as stem cells, having the capacity to differentiate into a wide variety of different cell types and e) abnormally closing/closed sutures and over-expression of Nell-1 in animals are restricted to calvarial bone. One skilled in the art would have reason to doubt Applicant's assertion that one could use stem cells and bone marrow cells can used in the claimed method of screening for an agent that modulates bone mineralization comprising contacting the osteogenic cell expressing the NELL-1 gene with a test agent when the cited art has taught that bone marrow and stem cells may not necessarily differentiate into osteogenic cells.

The specification fails to teach or disclose how bone marrow cells or stem cells can be used in the claimed method of screening for agents that modulate bone mineralization when these cells may not actually differentiate into osteogenic cells. There is not teaching or disclosure in the instant specification that shows a method of screening for an agent that modulates bone mineralization using bone marrow or stem cells.

Factors to be considered in determining whether undue experimentation is required are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

There is lack of enablement for the use of method for screening an agent that modulates bone mineralization wherein the method comprising contacting an osteogenic cell selected from the group consisting of a stem cell and a bone marrow

cell. Therefore, one of skill in the art could not conclude that the Nell-1 gene could be use to screen for agents that modulate bone mineralization using bone marrow cells or stem cells when the instant specification and the cited art teaches that Nell-1 may be associated with intramembraneous bone formation in fetal calvarial osteoblastic cells and bone marrow and stem cell do not necessarily differentiate into these types of cells. It is determined that there are no working examples commensurate with the claims that demonstrate that bone marrow and stem cell can be used in the claimed method. There is limited guidance provided in the specification as to how to use the claimed method since the cited art has taught that the precise signals that trigger differentiation down a particular path are not fully understood and there bone marrow and stem cells can differentiate into many other types of cells which are not osteogenic and osteogenic cell are required by the claimed method. The skilled artisan is forced into undue experimentation to practice (make and use) the invention as is broadly claimed.

Applicant disagrees with the Examiner's position. Applicant asserts that although the Zhang et al reference teaches that NELL-1 overexpression caused grossly visible anomalies in calvarial tissue and there were no visible anomalies seen in any other tissue does not automatically support the Examiner's position that no effect of mineralization was observed. Applicant urges that Zhang et al 's observation was restricted to calvarial bone. Applicant urges that to practice the claimed method, there is no requirement that a stem cell or a bone marrow cell can differentiate into an osterogenic cell. Applicant urges that they have cited references that provide evidence that stem cells or bone marrow cells under a certain set of conditions can differentiate into osteogenic cells.

Applicant's arguments filed June 7, 2005 have been fully considered but they are not persuasive. It is the Examiner's position that the scientific field in regard to stem cells and bone marrow cells differentiating into osterogenic cells is unpredictable, at best. Applicant admits in this response that "stem cells or bone marrow cells under a

certain set of conditions can differentiate into osteogenic cells". One of skill in the art could reasonable conclude that if "certain conditions" are required for stem cells and bone marrow cells to differentiate into osterogenic cell and when these conditions are not available, stem cells and bone marrow cells may differentiate into other types of cells. Therefore, it is the Examiner's position, that stem cells and bone marrow cells do not necessarily differentiate into osterogenic cells.

To address Applicant's comments that the claimed method does not require stem cells or bone cells. It should be remembered that the claimed method requires "osteogenic cells" and the instant specification has indicated that bone marrow cells and stem cells fall within the meaning of "osteogenic cells" (see page 4 and 8). Thus, one of skill in the art would reasonably conclude by the instant disclosure that the claimed method requires stem cells or bone marrow cells.

To address Applicant's comment's regarding Zhang et al, there is no evidence in the Zhang et al reference that teaches, suggests or discloses that cells other than calvarial cells are effected by the overexpression of NELL-1. Zhang et al teach that anomalies were restricted to calvarial bone, despite generalized, non-tissue-specific over-expression of Nell-1 (see the Abstract). Therefore, the claimed method requires calvarial bone cells. One of skill in the art would reasonably conclude that the instant specification does not reasonably provide enablement for the claimed method of "screening" for an agent that modulates bone mineralization, wherein the method comprising contacting an osteogenic cell selected from the group consisting of a stem

cell and a bone marrow cells. In view of the comments made above, the rejection set forth under 35 U.S.C. 112, first paragraph is maintained.

4. The rejection under 35 U.S.C. 112, first paragraph is maintained for claim 51 for the reasons set forth on page 8 paragraph 5 of the previous Office Action.

The rejection was on the grounds that claim 51 is rejected under 35 USC 112 second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention Claim 51 recites "wherein the osteogenic cell is selected from a cell endogenous to a fetal calvarial cell culture. It is unclear as to what Applicant is referring. Clarification is required.

Applicant urges that the claims has been amended and is now clear and definite.

It is still unclear as to what Applicant means by the recitation "wherein the osteogenic cell is endogenous to a fetal calvarial cell culture". Clarification is requested. Therefore, the rejection is maintained.

Claim Rejections - 35 USC § 112

New Ground of Rejection Necessitated by Amendment

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-2, 8-12 and 51-52 and 54 are rejected under 35 USC 112 second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite "a method for an agent that modulates..." . It is unclear as to what Applicant is referring. Does Applicant mean " a method for screening for an agent that modulates ...."? Clarification is required.

Status of Claims

6. No claims allowed.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

8. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 872-9306.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (571) 272-0857. The examiner can normally be reached on Monday – Friday from 9:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (571) 272-0864.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov./>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vanessa L. Ford
Biotechnology Patent Examiner
August 24, 2005

LYNETTE R. F. SMITH
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600